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REMARKS

The 36 original claims have been consolidated into 16 new claims, provided herewith in replacement sheets. These new claims are introduced to facilitate prosecution only and are not to be interpreted as an admission of the allegations made in the Written Opinion. No new matter is introduced and no new search is necessitated. All the new claims have specification support, e.g., in the claims as originally filed (particularly claim 21) and also pages 9-10, and 19-23 (Examples 5-11) of the specification. New claim 16 has a specific specification basis in Table 2, page 25, column 5, of the application. The word "system" has been inserted after "assay" in some of the claims to refer to the use of "assay" as a noun and not a verb. However, both usages find support generally in the specification, and the word "system" is therefore not considered to technically represent new matter.

Newly introduced claims 1-15 are drawn to cells, assay systems and methods for detecting and/or isolating virus, preferably primary virus, by amplifying the virus using an amplicon. Preferably the amplicon is Tat and the virus is HIV. However, those of skill know of other schemes, e.g., Tax and HTLV, that are also readily enabled per the invention. In preferred embodiments, the surface receptors CCR5, CXCR4, and CD4 are expressed by the cells and provide for infectivity of the virus prior to its amplification in the cell. In embodiments where an indicator cell is used, that indicator cell preferably also contains the same surface receptors to allow for infectivity, and must also contain a marker gene, preferably one selected from the group consisting of GFP, luciferase, Bgal, and antibiotic resistance.

Claim 16 is unobvious over Platt because Platt does not teach or suggest a method that makes use of a cell line for propagating primary HIV that has a greater infectivity than PMBC cells. Nor for that matter does the Ferguson patent teach such. In this regard, an error is noted in Table 2, page 25, column 5, for the value noted for primary HIV isolate IVED 1563. The incorrect value shows a "2.2E+4" whereas the true value should read "2.2E+5," thereby eliminating the anomaly in that column relative to new claim 16.

The new claims fortuitously moot the pending rejections against the original claims. The Written Opinion alleged a lack of enablement of original claims 10, 16, 11, 17, and 25 for failure to deposit the cell lines J53BL and J53 tat, an alleged lack of clarity of claims 1-12, 16, 17, 21, 23, 34,

35, and 36 for failure to distinguish methods from composition of matter claim form, an alleged lack of clarity of claims 16 and 17 for their recitation of "functional equivalents," an alleged lack of clarity for claim 21 for failure to recite a step different than claim 20, an alleged lack of clarity for claim 23 as relates to how virus recited therein is "amplified", an alleged lack of clarity for claims 34 and 35 as related to the phrase "use of," and an alleged lack of clarity for claim 36 for failure to recite any additional limitation(s). In addition to the preceding objections, claims 1-36 were alleged to lack an inventive step over Platt et al. (1998) J. Virol. 72:4, pp. 2855-2864 in view of Ferguson et al. (1991) US Patent 5,026,635. How these rejections are made moot by the new claims are discussed below.

Enablement of claims 10 , 11, 16, 17, and 25 as orginally filed

The rejection of these claims is made moot by their cancellation without prejudice. None of the new claims are directed to specific cell types that would necessitate a deposit.

Clarity of claims 1-9, 12, 21, 23, 34, 35, and 36

These claims were objected to for alleged lack of clarity in typifying a method or composition claim. The claim amendments recited above are respectfully submitted to overcome the rejection. The claims have been rewritten to more particularly distinguish between the two different types of claims.

Rejection for Alleged Lack of Inventive Step

Original claims 1-36 were also alleged to lack an inventive step over the reference Platt et al. (1998) J. Virol. 72:4, pp. 2855-2864 in view of Ferguson et al. (1991) US Patent 5,026,635.

The claims as amended recite the use of an amplicon for amplifying virus, as well as the use of a phenotypic marker for detecting the virus once it has been amplified. The virus is preferably a primary virus, more preferably HIV, the amplicon is preferably Tat which transcriptionally activates viral reproduction, and the marker gene is selected from the group consisting of antbiotic resistance genes (e.g., CAT), Bgal, luciferase, and GFP. The claims are novel because *inter alia* they permit the

amplification, detection, isolation, and characterization of primary virus isolates in a heretofore novel and sensitive fashion. The chemokine receptor characteristics of the amplicon and indicator cells (depending on the exact claim embodiment) contribute to the invention's utility by providing for ready infectivity that simulates natural infection of primary peripheral blood mononuclear cells (PBMC). An additional advantage is use of the system in determining resistance, with the caveat that different, or combinations, of drugs may be conveniently screened and rated for effect with this system. Other merits are taught in the specification as filed.

Platt, et al. (1998) J. Virol. 72:4, pp. 2855-2864

Platt, et al. teach the effects of CCR5, CXCR4, and CD4 cell surface co-receptor concentrations on HIV infectivity. Platt, et al. used Hela-derived cells to demonstrate this. Platt, et al. further teach the *potential* use of these co-receptor expressing cells for quantitating and titering primary viral isolates from patients. Platt et al further teach these cells' further use in drug and neutralization testing. Platt et al. in no way teach or suggest the use of an amplicon mechanism and implement for boosting viral concentration and improving assay sensitivity.

Ferguson et al. (1991) US Patent 5,026,635

Ferguson et al. teach an HIV reporter system wherein a single mammalian cell line is engineered to possess two different heterologous coding sequences, one that constitutes a reporter gene, and another that encodes a trans-activating regulatory protein, i.e., Tat, that serves to specifically activate the reporter. Ferguson et al. teaches that the system can be used to screen and identify potential anti-HIV drugs directed against the specific HIV gene product, Tat. The system is illustrated in Figure 1. The title of the patent, "STABLE HUMAN CELL LINES EXPRESSING AN INDICATOR GENE PRODUCT UNDER VIRUS-SPECIFIC GENETIC CONTROLS," is consistent with this teaching. Further illustrative is the discussion at column 2, lines 33-35: "The present invention provides a system that allows for rapid screening and identification of compounds that *specifically interfere with HIV tat* function." (emphasis added). Ferguson et al further teach that the system can be broadened to encompass other specific positive-acting or negative-acting

regulators of viral gene expression. Id at ll. 39-50. The Examples and claims of this patent are all directed to inhibitors of Tat.

Nowhere does Ferguson teach or suggest the use of an amplicon for propagating, i.e., amplifying, isolating, titering, and/or further characterizing or manipulating whole virus. In fact, Ferguson's use of Tat is entirely de-coupled from the natural viral biology. The only vestige remaining is the interaction of Tat with the cis-acting sequence which controls reporter genev expression.. It is the whole point of the instant invention to provide a novel method and assay system for propagating virus, preferably whole primary virus.

Thus, even combining the teachings of Ferguson and Platt does not suggest the inventive step of providing an amplicon for propagating virus and/or the use of a cell having a greater infectivity to primary HIV than do PMBC cells.

Respectfully submitted,

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Table 2. Comparison of HIV- I isolate infectivity in different cell types

HIV-1 isolate	HeLa-CD4 (MAGI cells)	HeLa-CD4-CCR5 (P4 cells)	H9 CD4-CCR5 (Hi5 cells)	HeLa-CD4-CCR5 (J53-CI6)	PBMC	Syncytia phenotype
IVED 1563	2.10E+02	2.24E+03	<1.2E+2	2.2E+5	1.84E+05	NSI
SHTI 2045	2.00E+01	5.72E+02	2.88E+03	1.2E+5	4.58E+04	SI
RIJA 0676	1.50E+01	1.68E+02	<1.2E+2	4.5E+5	1.84E+05	SI
ELRA 1452	1.50E+01	1.00E+02	<1.2E+2	9.5E+5	4.58E+04	NSI
JAME 2457	5.00E+00	4.00E+00	<1.2E+2	1.8E+5	4.58E+04	SI
WOAL 0263	1.80E+01	5.40E+02	<1.2E+2	8.5E+4	4.58E+04	SI
WIMI 2294	2.10E+01	1.52E+02	<1.2E+2	4.53+4	1.15E+04	SI
DAKE 2205	6.20E+01	3.28E+02	<1.2E+2	1.1E+5	4.58E+04	NSI
BARE 1219	1.80E+01	4.48E+02	<1.2E+2	1.3E+5	4.58E+04	NSI
SMBA 1685	2.20E+01	6.40E+01	<1.2E+2	1.1E+5	4.58E+04	SI
TIVI 2007	8.90E+01	4.60E+02	<1.2E+2	4.1E+5	1.84E+05	SI
SWBA 1427	2.80E+01	4.48E+02	<1.2E+2	9.0E+4	4.58E+04	NSI
CHVI 2467	5.00E+01	4.00E+00	<1.2E+2	3.8E+4	1.15E+04	SI
VIJE 1945	7.80E+01	3.04E+02	2.88E+03	2.1E+5	4.58E+04	NSI
DECH	1.20E+01	2.00E+01	<1.2E+2	1.2E+5	4.58E+04	NSI
SHCH	1.80E+02	1.76E+04	<1.2E+2	3.6E+5	4.58E+04	NSI
PELE 1256	1.20E+01	2.40E+01	2.88E+03	1.0E+5	1.15E+04	SI
KEWI 2431	1.90E+03	4.54E+05	<1.2E+2	2.0E+5	4.58E+04	NSI
MADA 2442	2.00E+01	1.40E+03	<1.2E+2	2.8E+5	4.58E+04	NSI
VATE 2328	2.00E+01	3.76E+02	<1.2E+2	4.5E+4	1.15E+04	SI
SG3-293T	2.20E+05	1.89E+05	1.84E+05	2.0E+5	1.84E+05	SI
YU-2-293T	0.00E+00	3.50E+05	4.58E+04	5.9E+4	7.36E+05	NSI